Respiratory phase resetting and airflow changes induced by swallowing in humans

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1. Relationships between the timing of respiration and deglutition were studied in thirty awake healthy subjects at rest. Deglutition was monitored by submental electromyography, pharyngeal manometry and videofluoroscopy. Respiration was recorded by measurement of oronasal airflow and chest wall movement. Three types of deglutition were studied: injected bolus swallows, spontaneous swallows, and visually cued swallows of boluses previously placed in the mouth.

2. The effect of each swallow on respiratory rhythm was characterized by measurement of cophase, defined as the interval between the onset of deglutitive submental EMG activity to the onset of subsequent rescheduled inspirations. Cophase was determined for swallows initiated at different phases of the respiratory cycle. In all subjects deglutition caused phase resetting of respiratory rhythm. Cophase was largest for swallows initiated near the inspiratory–expiratory (I–E) transition and smallest for swallows initiated near the expiratory–inspiratory (E–I) transition. The pattern of respiratory resetting by deglutition was topologically classified as type 0. This pattern was shown for swallows induced by bolus injection or visual cue, and for spontaneous swallows.

3. The incidence of spontaneous deglutition was influenced by the position of the swallow in the respiratory cycle. Few spontaneous swallows were initiated near the E–I transition whereas most occurred from late inspiration to mid-expiration.

4. Deglutition caused an abrupt decrease in airflow leading to an interval of apnoea, followed by a period of expiration. The duration of deglutition apnoea for spontaneous swallows was shorter than that for 5 ml bolus swallows, and was unaffected by the respiratory phase of swallow initiation. The period of expiration after swallowing was longest for swallows initiated at the I–E transition, and shortest for E–I swallows.

5. The intervals between bolus injection and the onset of deglutition apnoea, and the timing of swallowing events, were not significantly altered by the phase in the respiratory cycle at which swallowing was exhibited.

6. To quantify the relationship between bolus flow and respiration, we determined the latencies between cessation of inspiratory airflow and arrival of the bolus at the larynx (α), and between laryngeal bolus departure and resumption of inspiratory airflow (δ). Both values were dependent upon the respiratory phase of swallowing. The lowest values for α and δ were found for early-inspiratory and late-expiratory swallows, respectively.

7. We conclude that swallowing causes respiratory phase resetting with a pattern that is characteristic of the strong perturbations of an attractor-cycle oscillator. The threshold for initiation of swallowing in awake subjects is influenced by, but not strongly coupled to, the phase of respiration. We propose that respiratory timing, in addition to anatomical barriers within the upper airway, influences the vulnerability for aspiration during deglutition. Swallows initiated near the E–I transition may be the most likely to result in bolus aspiration, especially in pathological conditions that weaken the impact of swallowing on respiratory rhythm or slow the transport of the bolus through the pharynx.

The pharynx in most mammals is a shared conduit for swallowing and respiration. This anatomical configuration allows for the possibility of aspiration of material into the airway during bolus passage. Several mechanisms minimize the risk of aspiration. It is well recognized that adduction of vocal and vestibular folds serves as a mechanical barrier during deglutition (Ardran & Kemp, 1952; Dodds, Stewart & Logemann, 1990); aspiration is possible if laryngeal closure is not maintained for the entire duration of laryngeal exposure to the swallowed bolus. In addition, exposure of the laryngeal aditus to the descending bolus is minimized by anterior rotation and rapid elevation of the larynx, lowering of the epiglottis over the aditus, bolus passage away from the aditus to the laterally located piriform recesses and timely relaxation of the cricopharyngeaus to allow the bolus to enter the oesophagus (Hollinshead, 1974; Dodds *et al.* 1990).

A less understood mechanism of airway protection involves the co-ordination of deglutition with the phasic activity of respiration. Protection of the airway from aspiration requires inhibition of inspiratory airflow throughout the period of laryngeal exposure to the swallowed bolus. This respiratory inhibition is called deglutition apnoea and appears to be a universal accompaniment of the normal swallow sequence in man (Clark, 1920; Wilson, Thach, Brouillette & Abu-Osba, 1981; Nishino, Yonezawa & Honda, 1985; Smith, Wolkove, Colacone & Kreisman, 1989; Selley, Flack, Ellis & Brooks, 1989; Nishino & Hiraga, 1991; Shaker *et al.* 1992; Issa & Porostocky, 1994).

The purpose of the present study was to evaluate, in awake healthy subjects at rest, relationships between timing of respiratory rhythm and deglutition. We analysed these interactions using different methods of swallow induction, and varied bolus volumes and densities. The following questions were addressed. Does deglutition alter the rhythmicity, i.e. cause phase resetting, of the respiratory rhythm generator, or are the alterations in respiratory timing due only to changes in the respiratory output system? Is the duration of deglutition apnoea and the time to the subsequent inspiration influenced by the timing of deglutition within the respiratory cycle? Is the swallow sequence itself influenced by respiration?

We found in all subjects that deglutition caused a characteristic pattern of phase resetting of respiratory rhythm. The swallow sequence and the duration of deglutition apnoea were not influenced by the respiratory phase. However, the latency between swallow events and onset of the subsequent inspiration was dependent upon the time of initiation of the swallow relative to the respiratory cycle; the shortest intervals were associated with late expiratory swallows. Our findings suggest that respiratory timing, in addition to anatomical barriers within the upper airway, influences the vulnerability for aspiration during deglutition.

METHODS

Experiments were performed in thirty healthy subjects (15 female, 15 male; aged 19–45). They were told about the various procedures that would take place but were not informed about the study's specific aims. Exclusion criteria included a history of dysphagia, aspiration and pulmonary or neurological disorders, and, for women, delayed menstruation or positive urine β-human chorionic gonadotrophin (β-HCG) (test performed less than 48 h prior to the study). Written informed consent was obtained from all subjects. The protocol was approved by the Research/Human Subjects Committee of St Elizabeth's Hospital of Boston where all studies were carried out.

Swallow induction

All subjects were studied while at rest in the sitting position. Three different methods of swallow induction were used. (1) In eight subjects, 5 ml boluses of liquid barium were injected using an automated pressure injector (Barber-Colman, Rockford, IL, USA) which was triggered by the investigator at various times in the respiratory cycle. The fluid was injected through rigid tubing which passed through the face mask and was attached to a flexible straw. The end of this straw was sealed and a 0·5 cm port was created in the distal segment. The position of the straw was adjusted with the port on the surface of the tongue, approximately 3 cm from the lower incisors. Fluoroscopic evaluation confirmed that injected liquid barium flowed onto the tongue and did not contact the posterior pharynx prior to initiation of swallowing. Measurement of the pressure within the rigid tubing demonstrated that the duration of injection was 715 ± 214 ms (mean $\pm$ S.D.). There were no significant differences between subjects. Each subject had been instructed to swallow the fluid as soon as it was presented. (2) In the same group of eight subjects, spontaneous swallows were also studied. These were recorded during the same experiment in which bolus injections were performed. In two subjects (O.S. and J.H.), the rate of spontaneous swallowing was increased by slow continuous infusion of water (4–6 ml min^{-1}) through the mouthpiece. (3) In a separate series of twenty-two subjects, boluses were manually delivered to the mouth with a syringe and held by the subject for 20–30 s until they were cued by the investigator to swallow. The cue was a red light-emitting diode, positioned 1 m in front of the subject, which was turned on for 0·5 s at various times in the respiratory cycle. In fifteen subjects the bolus was liquid (water in 9 subjects; barium in 6 subjects) of different volumes (2, 5 or 10 ml) and in seven subjects, 5 ml barium of different densities (liquid in 7 subjects; cream in 4 subjects; paste in 3 subjects) were given.

An attempt was made in all experiments to minimize the effects of sound generated by the bolus injector and fluoroscopic equipment. Subjects were either exposed to 80 dB white noise through headphones, or received foam ear plugs. Both methods were satisfactory; there was no change in respiratory pattern associated with activation of the fluoroscope or the bolus injector in control trials in which no fluid was injected.

Synchronized intrapharyngeal manometry and videofluoroscopy

Twenty subjects underwent concurrent manometric and videofluoroscopic studies of swallowing for specific volumes of barium liquid (40% w/v; E-Z-EM Inc., Westbury, NY, USA), barium cream (100% w/v; Rorer Pharmaceuticals Co., Fort Washington, PA, USA), and/or barium paste (120% w/v; E-Z-

EM Inc.). Each subject was seated and positioned laterally relative to the image intensifier. All subjects undergoing fluoroscopy wore a lap shield, and total exposure time did not exceed 180 s per subject. Fluoroscopic images were recorded at 30 frames per second on a VHS videocassette recorder (Panasonic model AG-7300) with frame-by-frame playback capability. Manometric and video recordings were synchronized through the use of an electronic timer (Thalner Electronics, USA) which superimposed digital timing information in hundreths of a second onto individual videoframes and transmitted a 5 ms square wave pulse at 1 s intervals to a multichannel thermal writing chart recorder (Gould Electronics, USA) or a digital data acquisition system (DATAQ Instruments, Akron, OH, USA; sample rate set at 350 Hz per channel) and IBM-compatible computer (Newton Personal Computers, Newton, MA, USA). In this way, the timing of fluoroscopic events related to swallowing was analysed with respect to the respiratory, electromyographic and manometric recordings.

Intrapharyngeal manometry was performed using a 1·8 mm catheter (Medical Measurements Inc., Hackensack, NJ, USA) in which three strain gauges (90% rise time < 100 μs) were mounted at 3 cm intervals. The catheter was passed transnasally after application of 2% xylocaine lubrication and positioned with the most distal recording sensor facing posteriorly at the cricopharyngeal sphincter, and the proximal leads at 3 and 6 cm above the sphincter, respectively (Maddock & Gilbert, 1993). Data acquisition was started at least 30 min after placement of the catheter, allowing for stabilization of the pharyngeal recordings.

Submental electromyography

In all subjects, surface electrodes were placed over the anterior suprahyoid muscle complex approximately 1 cm posterior to the chin symphysis in the mid-line. The signal was filtered (Pre-Amp PAG3T, Teca Co., USA), amplified (TE42 EMG, Teca Co.), whole-wave rectified and integrated (13-g4615-70, Gould Electronics, USA) at 50 ms intervals, and recorded.

Airflow and chest wall movement

Airflow through the mouth and nose was measured using a face mask (Hans Rudolph Inc., USA), pneumotachograph (Fleish, USA; 90% rise time < 10 ms), and differential pressure tranducer (Medical Measurements, USA; 90% rise time < 200 μs). The dead space of the system was 150 ml. Zero flow was established by voluntary breath-holding or by removing the pneumotachograph from the face mask. Tidal volume was calculated from the airflow signal using mathematical integration software (DATAQ Instruments). A 3 l syringe was used for volumetric calibration; known volumes of air were passed through the pneumotachograph at different rates and in opposite directions. Within the experimental range of airflow measurements, the integrated airflow signal was linearly related to volume ($r > 0{\cdot}95$). Chest wall movement was monitored by the measurement of pressure changes within a flexible tube fitted about the upper chest approximately 12 cm below the sternal notch. All subjects breathed ambient air at rest.

In our experiments on the effects of changing bolus volume and density, respiratory rhythm was studied by measurement of chest wall movement. In control studies of simultaneous chest wall movement and airflow measurements, we digitized the onset of inspiration using both methods for 786 breaths in two subjects. The measurements were made independent of each other, in order to avoid observer bias. We found that the onset of outward chest wall movement was a reliable marker of inspiration; on average it lagged behind the onset of inspiratory airflow by $14 \pm 0{\cdot}8$ ms (mean $\pm$ S.E.M.). Therefore, either method was reliable for measurement of phase resetting of respiratory rhythm. However, measurement of chest wall movement did not accurately identify the onset of expiration or the period of deglutition apnoea.

Experimental protocols

We studied interactions between swallowing and respiration by applying three protocols, corresponding to the three methods of swallow induction.

Firstly, in eight subjects, we recorded the respiratory responses to swallows induced by pressure-injected 5 ml boluses of liquid barium ($n = 186$ swallows). Figure 1 provides an example in one subject of fluoroscopic events relevant to swallowing, and simultaneous manometric and respiratory recordings. Secondly, in these same subjects we measured the respiratory changes due to spontaneous swallows ($n = 218$ swallows). The average spontaneous swallow frequency was 2 min^{-1}. In two subjects (O.S. and J.H.), continuous infusion of sterile water at a rate 4–6 ml min^{-1} increased the average swallow frequency to 4·5 min^{-1}. Of the 218 recorded spontaneous swallows, 126 were from these two subjects. Pharyngeal manometry was recorded and onset of submental electroyographic (EMG) activity was used to determine the timing of each swallow relative to the respiratory cycle. Thirdly, in twenty-two subjects, we studied respiratory phase resetting patterns for different bolus properties. Fifteen subjects were cued visually to swallow boluses of different volumes (2, 5 and 10 ml) of water (9 subjects, $n = 429$ swallows) or liquid barium (6 subjects, $n = 221$ swallows). Seven subjects were similarly cued to swallow barium boluses of different densities (5 ml liquid, 7 subjects, $n = 108$ swallows; 5 ml cream, 4 subjects, $n = 54$ swallows; 5 ml paste, 3 subjects, $n = 57$ swallows). One subject in this group could not be studied because of excessive nausea after swallowing barium cream. The swallows were evaluated with pharyngeal manometry and videofluoroscopy of the oropharynx.

Data handling

Data were excluded for runs having more than one swallow immediately following the cue or bolus injection. Such multiple swallows were seen in less than 5% of the experimental runs.

The video recordings were analysed in slow motion and by single-frame analysis using the playback capabilities of the video recorder. Onsets of superior and anterior hyoid movement, and laryngeal bolus exposure time (bolus head arrival to bolus tail departure at the level of the laryngeal aditus) were determined from the digital clock display on each video frame. For each swallow, a time line of these fluoroscopic events was indicated on the recordings. Individual videofluoroscopic, manometric, EMG and respiratory events were digitized by computer. For analog tracings, a tablet (Numonics Model 2210, USA) and software (SigmaScan 3.94, Jandel Scientific, USA) were used. Digitally acquired recordings were analysed directly using playback software (DATAQ Instruments) with export of digitized data to spreadsheet software (Excel, Microsoft Inc., USA). The onset of the swallow was indicated by the onset of integrated EMG activity, which has been termed the 'leading complex' of

deglutition (Doty & Bosma, 1956). The end of the pharyngeal phase of swallowing was marked as the termination of the constrictor wave at the hypopharyngeal sensor of the pharyngeal catheter, which was usually seen just after the departure of the bolus from the hypopharynx. Laryngeal bolus exposure was determined by tracking the time lapse between arrival of the bolus head at, and departure of the bolus tail from, the laryngeal aditus.

Statistical inferences were based on analysis of group mean differences with the Student's unpaired t test, or the Student's paired t test for comparison of differences within each subject. A Bonferroni correction was applied when making multiple comparisons of the same group of measurements. Means are given ± S.E.M. unless otherwise stated.

Phase resetting analysis

Certain definitions were used for analysis of the respiratory resetting patterns that follow deglutition. These are illustrated in the airflow and EMG tracings of Fig. 1, and are identical to the standard definitions applied to other biological oscillators (Winfree, 1977; Winfree, 1980, chap. 1; Paydarfar, Eldridge & Kiley, 1986). Old phase (ϕ) was defined as the time from inspiratory onset to onset of the rapid rise in submental EMG activity associated with swallowing. Cophase (θ) of the first reset breath was the time from the EMG onset to the onset of the first inspiration following the swallow. The cophase of subsequent breaths was likewise measured relative to EMG onset. The resulting data were normalized by assigning a value of one to the average period of three control breaths preceding the swallow. Thus, old phase and cophase were expressed as fractions of one cycle rather than units of time. At least five breaths were allowed to elapse after each swallow before recording the next run of three control breaths. We should point out that the interval between any marker of deglutition and reset respiratory timing is a valid measure of cophase, provided that the markers are applied consistently in a given experiment.

Using the present definitions, the effect of swallowing on the first normalized respiratory cycle length can be determined by adding ϕ and θ of the first breath after the swallow. If the swallow had no effect on respiratory timing of the first breath then $\phi + \theta = 1$ for stimuli given at all times in the respiratory cycle, and a plot of cophase against old phase would be defined by $\theta = -\phi + 1$. For the nth breath after the swallow, lack of

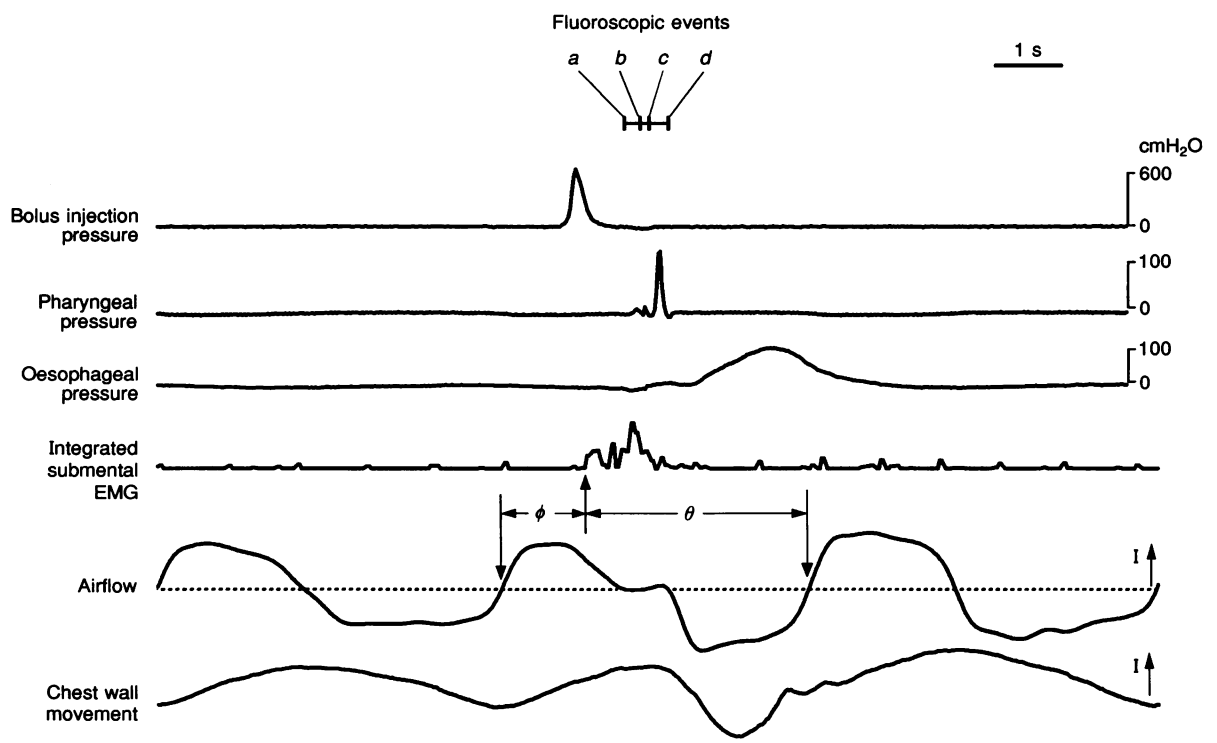

Figure 1. Experimental methods and definitions

Example of swallowing and respiratory recordings in one subject who swallowed 5 ml liquid barium after bolus injection. Fluoroscopic events are: *a*, onset of superior hyoid movement; *b*, onset of anterior hyoid movement; *c*, arrival of bolus head at the laryngeal aditus; *d*, departure of bolus tail from the laryngeal aditus. Old phase (ϕ) and cophase (θ) are normalized to the mean period of 3 control breaths prior to deglutition. Bolus pressure is recorded at the end of injection tubing near the inlet to the mouth. Pharyngeal pressure is measured adjacent to the laryngeal aditus. The horizontal dotted line through airflow tracing represents zero flow, deflection above this line, and upward deflection of the chest wall recording, represent inspiration (I↑).

phase resetting would be predicted by the relationship $\theta_n = -\phi + n$. Deviations from this relationship are suggestive of phase resetting. In the example shown in Fig. 1, $\phi + \theta$ is less than one, indicating that the swallow shortened the cycle length. In order to show that phase resetting had taken place, it would be necessary to demonstrate that changes in cycle length shift the timing of all breaths after the swallow, when compared with the control rhythm before the swallow.

RESULTS

Effects of swallowing on respiratory rhythm

In eight subjects, we studied the respiratory responses, measured as airflow and chest wall movement, to swallowing 5 ml of liquid barium, injected at different phases of the respiratory cycle. Figure 2*A* shows six of twenty-eight runs in one subject, and demonstrates the

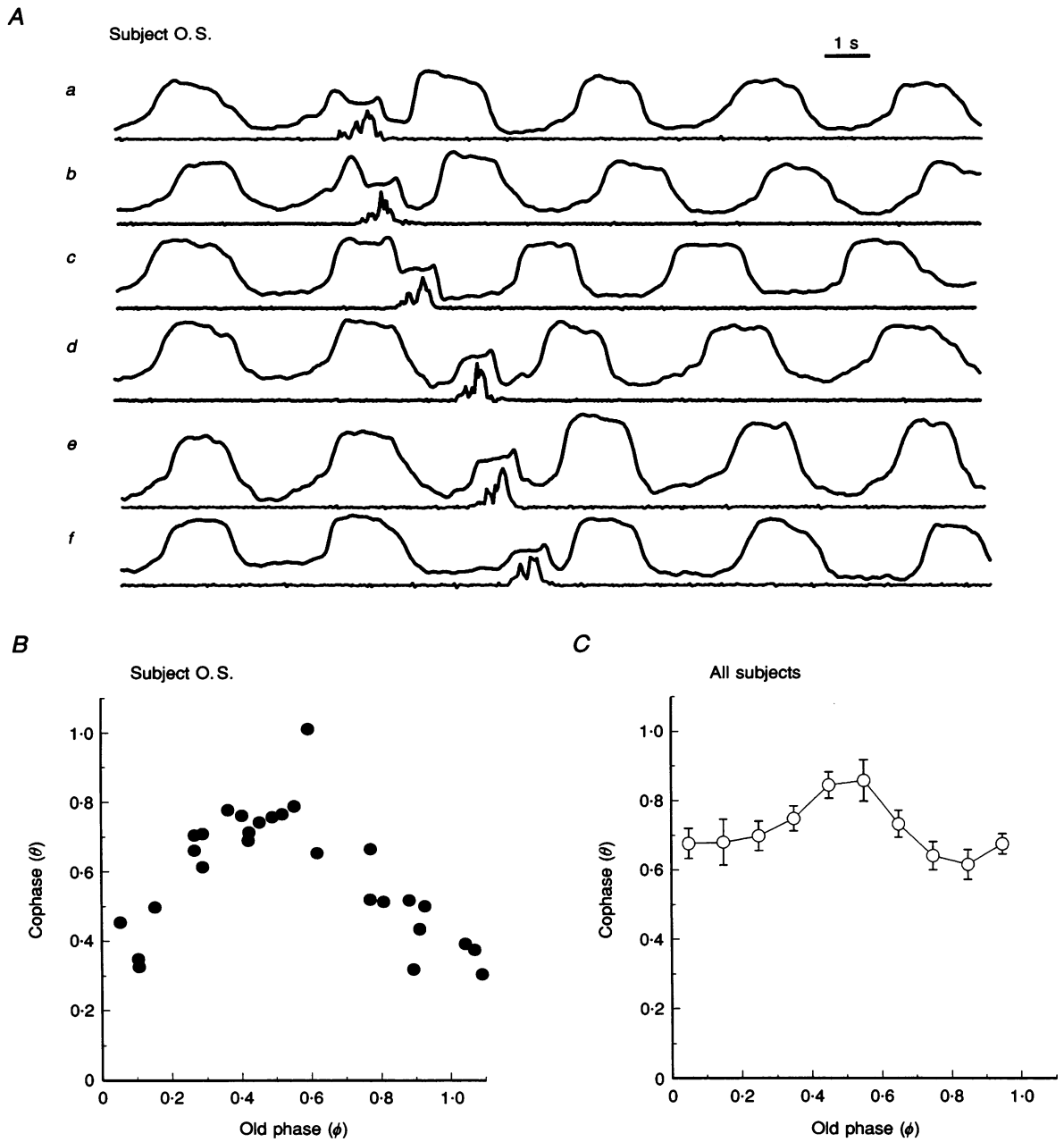

Figure 2. Effect of swallowing on respiratory rhythm

A, airflow and integrated submental EMG activity for 6 runs (*a–f*) in subject O.S. *B*, plots of cophase (θ) *vs.* old phase (ϕ) for subject O.S. *C*, the pooled data for 8 subjects who received bolus injections. All subjects showed rise and fall in cophase, with trough values near the E–I transition.

pattern of respiratory airflow changes and phase resetting that was typical for all subjects. Increased EMG activity was associated with rapid decrease in airflow to an interval of apnoea, followed by a variable period of expiratory airflow. This overall response was seen for swallows initiated during inspiration (runs *a–c*) and during expiration (runs *d–f*). The interval between onsets of EMG and the first inspiration after the swallow progressively increased as the swallow appeared later in the inspiratory phase, then decreased as the swallow appeared later in the expiratory phase. Figure 2*B* illustrates the plot of cophase *versus* old phase for all twenty-eight runs in this subject and Fig. 2*C* illustrates the pooled data for all eight subjects. Cophase increases then decreases, with maximum values for swallows that were initiated near the inspiratory–expiratory (I–E) phase transition ($\phi = 0{\cdot}43 \pm 0{\cdot}12$, mean ± S.D.), and minimum values for swallows initiated near the expiratory–inspiratory (E–I) phase transition.

In Fig. 3, we show the resetting plot for the same subject as in Fig. 2 (O.S.) and in another subject (J.H.), with cophases plotted for the first three breaths after the swallow. The resetting pattern persists for the subsequent breaths, demonstrating that the alteration in respiratory timing induced by swallowing represents a true resetting of respiratory rhythmicity, and thence the central respiratory oscillator. It is noteworthy that although the pattern of resetting was similar in all subjects, each subject had a unique pattern, reflecting the magnitude of change in cophase from the trough level at the E–I transition to the peak level at the I–E transition.

In the examples shown in Fig. 3, cophase increases then decreases but has a net change of zero. The pattern strongly deviates from the plot that would be expected for no resetting. If there had been only a transient alteration in the timing of the respiratory output system without a shift in the rhythm generator, the plot of cophase *versus* old phase for the second and third breaths after swallowing would have depicted a line with slope −1 (see Methods). Old phase corresponding to early inspiration was replotted across the E–I transition to demonstrate the continuity of data points across the full cycle. A net cophase change of zero and apparent continuity of data across the respiratory cycle were found in all subjects. These findings fulfil the topological definition of type 0 resetting (Winfree, 1977; Winfree, 1980, chap. 1).

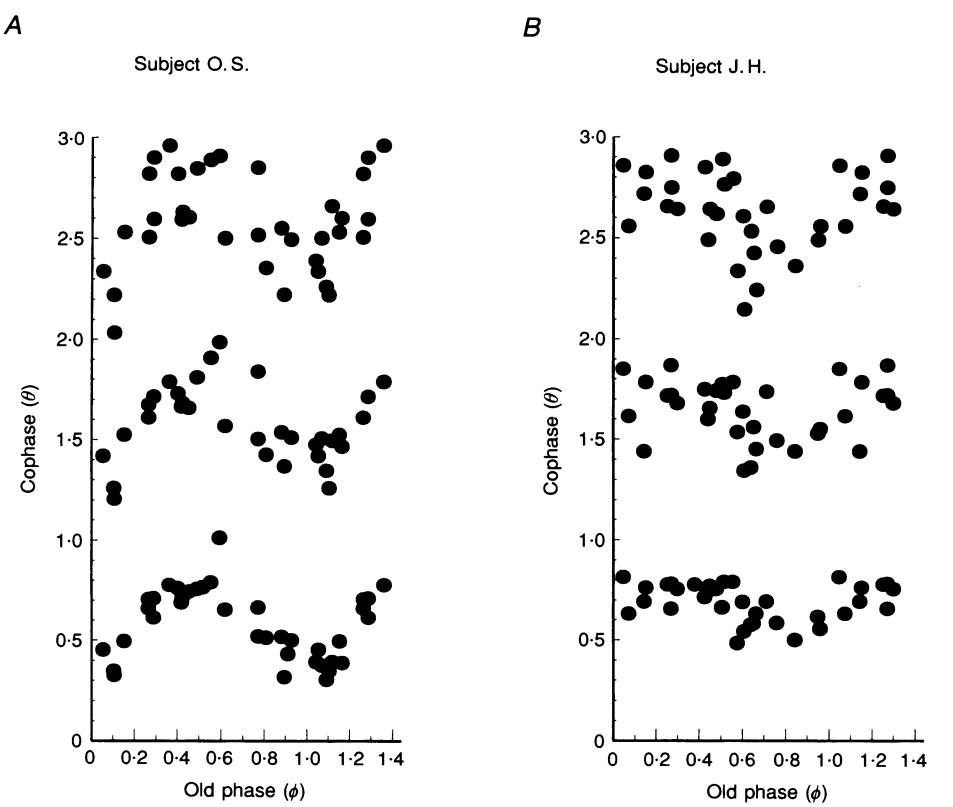

Figure 3. Resetting plots for three breaths after swallowing in two subjects

Cophase (θ) has a net change of zero over the full cycle of old phase (ϕ). The pattern of phase resetting persists for the 3 breaths shown. Note that although the plots in the 2 subjects are similar, with trough cophases near the E–I transition, the amount of cophase variation is less in subject J.H.

We found the type 0 pattern for a broad range of bolus volumes and densities. Figure 4*A* shows the results of changing bolus volume in one subject, typical of the findings in all fifteen subjects who were visually cued to swallow fluid boluses of different volumes. Volumes of 2 and 10 ml water caused the same type 0 pattern in this subject, showing a rise and fall in cophase with increases in old phase. There was no effect on cophase of changing bolus volume (2, 5 and 10 ml) in any of the fifteen subjects (water swallows, 9 subjects; barium swallows, 6 subjects) or in the pooled data of subjects swallowing water ($n = 429$ swallows) or barium ($n = 221$ swallows). The mean cophase (15 subjects, 650 swallows) for the first half-cycle was $0{\cdot}77 \pm 0{\cdot}02$ for 2 ml, $0{\cdot}68 \pm 0{\cdot}02$ for 5 ml and $0{\cdot}75 \pm 0{\cdot}02$ for 10 ml boluses ($P > 0{\cdot}05$). The mean cophase for the second half-cycle was $0{\cdot}58 \pm 0{\cdot}03$ for 2 ml, $0{\cdot}51 \pm 0{\cdot}02$ for 5 ml and $0{\cdot}58 \pm 0{\cdot}02$ for 10 ml boluses ($P > 0{\cdot}05$). In the six subjects who swallowed liquid barium, fluoroscopic evaluation was performed ($n = 110$ swallows), which showed that each had a small increase in laryngeal exposure time

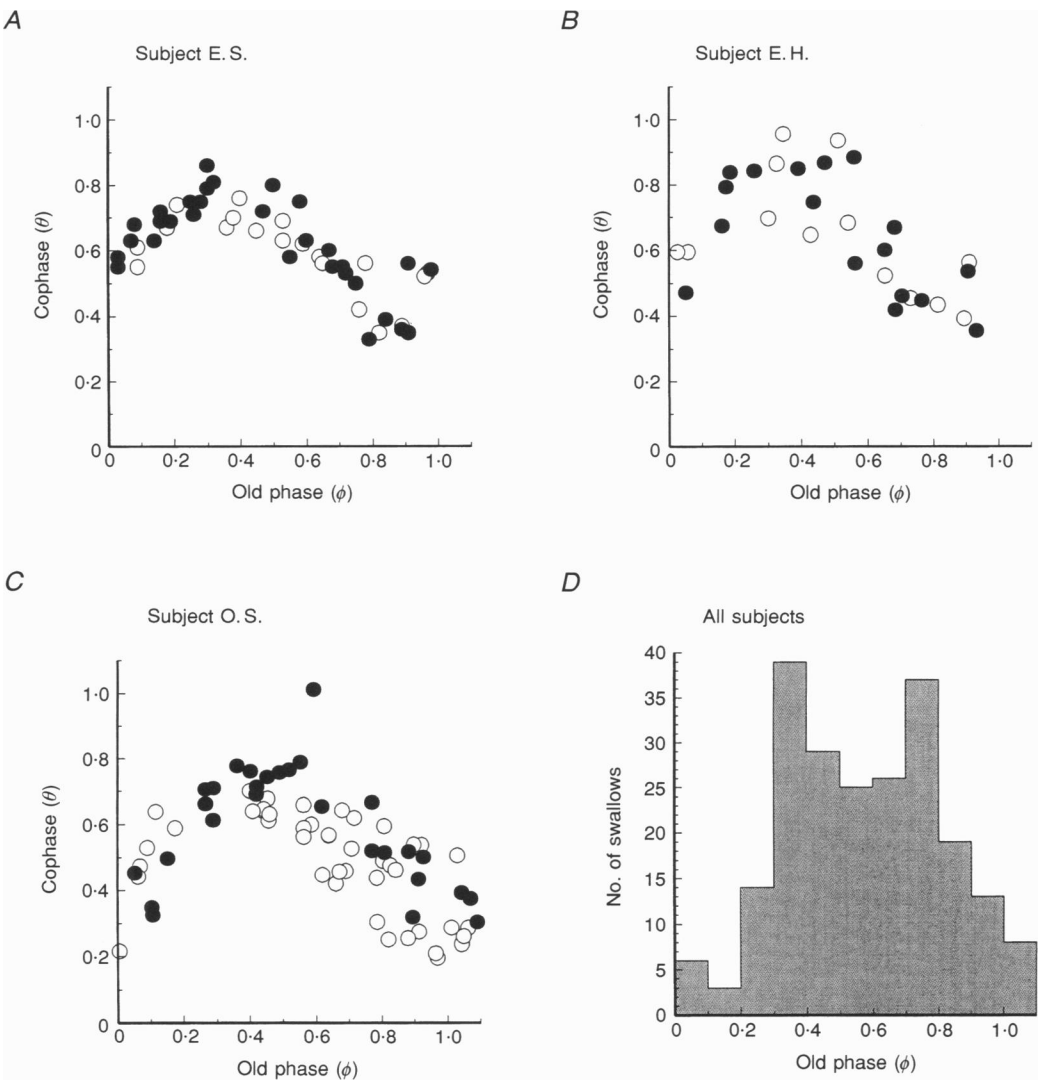

Figure 4. Effect of changing bolus volume, density and method of initiation of swallowing on respiratory phase resetting

Resetting plots for swallows of *A*, different bolus volumes: ●, 2 ml water; ○, 10 ml water; *B*, different bolus densities: ●, barium liquid; ○, barium paste. *C*, resetting plots for spontaneous and 5 ml bolus swallows: ●, 5 ml water; ○, spontaneous during 4 ml min^{-1} continuous water infusion. All plots show type 0 resetting of respiratory rhythm. *D*, incidence of spontaneous swallows initiated at different old phases (ϕ), showing low incidence of spontaneous swallowing in late expiration and early inspiration relative to other phases of the respiratory cycle. The I–E transition corresponds to an old phase of $0{\cdot}42 \pm 0{\cdot}07$ (mean ± S.D.).

associated with boluses of 10 ml compared with 2 ml of liquid barium (mean increase 34 ms, range 4–52 ms; $P = 0{\cdot}015$).

In another six subjects, deglutitive respiratory resetting patterns were compared for 5 ml boluses of varying density: barium liquid (40% w/v) *versus* barium cream (100% w/v) or barium paste (120% w/v). Figure 4*B* shows an example in one subject. The resetting patterns due to liquid and paste swallows are type 0, and show no appreciable difference. The deglutitive respiratory resetting patterns for the liquid *versus* cream swallows were also indistinguishable.

Figure 4*C* shows the resetting pattern in one subject who swallowed spontaneously while water was infused continuously at a rate of 4 ml min^{-1} (○) and in response to injected 5 ml water boluses (●). Both experiments led to the type 0 pattern. There was a tendency for slightly shorter cophases with spontaneous swallows when compared with bolus swallows (see airflow changes, below). The likelihood of spontaneous swallowing was not the same for all phases of swallow initiation. There were few swallows initiated near the the E–I transition; most spontaneous swallows were initiated in late inspiration to mid-expiration. Figure 4*D* shows the frequency distribution, relative to old phase, of all 218 spontaneous swallows recorded in eight subjects. The frequency distribution for spontaneous swallows without or with slow water infusion was the same. In contrast, bolus injection or visual cueing led to activation of the swallow sequence after a fixed latency that was not dependent upon the respiratory phase. Nevertheless, all methods of swallow initiation (pressure injection, visual cueing and spontaneous) resulted in type 0 respiratory resetting.

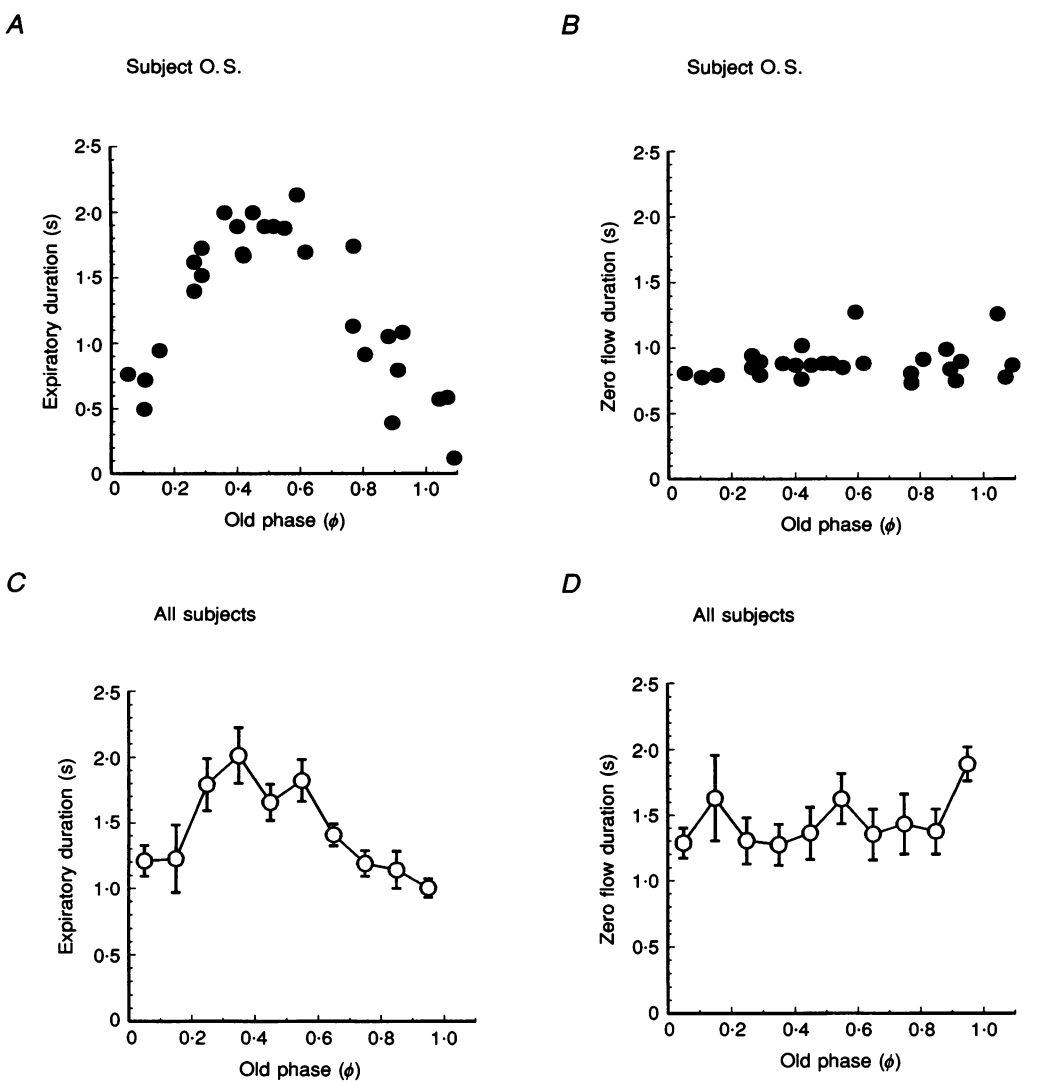

Figure 5. Durations of expiration after, and apnoea during, deglutition

A and *B*, results for subject O.S. *C* and *D*, results for all 8 subjects. The interval of expiration is longest for I–E swallows and shortest for E–I swallows. Deglutition apnoea is relatively unaffected by the respiratory phase of swallowing.

Airflow changes associated with swallowing

Airflow changes during swallowing were recorded in eight subjects. In these experiments, swallowing was induced by pressure injection of 5 ml liquid barium. We also analysed the airflow changes associated with spontaneous swallows in the same subjects. Swallowing was associated with sequential respiratory airflow alterations that appeared in three phases: (1) an initial rapid decrease in airflow to zero, associated with the onset of submental EMG activity; (2) an interval of zero airflow during most of the swallow sequence; and (3) an interval of expiratory airflow after the swallow. Examples are shown in Figs 1 and 2. There was a brief (189 ± 57 ms, mean ± S.D.) interval of 'inspiratory' airflow at the end of the zero flow interval, corresponding to a small volume (9 ± 5 ml, mean ± S.D., control tidal volume 400 ± 68 ml, mean ± S.D.). Fluoroscopic analysis suggested that the pharynx filled with air but the glottis was still closed during this interval. The magnitude and duration of this interval for spontaneous and bolus swallows were indistinguishable.

Figure 5 shows the relationship between the airflow intervals associated with 5 ml bolus swallows and the time of the swallow relative to the respiratory cycle (old phase). Figure 5*A* and *B* shows results in one subject (O.S.). As the swallow occurs progressively later in the respiratory cycle, the expiratory interval after the swallow rises, peaks for swallows initiated at the I–E transition, and falls. In contrast, the zero flow interval is relatively unaffected by the timing of the swallow relative to the respiratory cycle. All subjects showed these relationships although the difference between maximum and minimum expiratory intervals varied from subject to subject. Figure 5*C* and *D* shows the mean data for each 0·1 interval of old phase in all eight subjects. The results in Fig. 5, when compared with Figs 2 and 3, suggest that the changes in cophase with respect to old phase are due mainly to changes in the expiratory interval. These changes also reflect the volume expired after each swallow. Figure 6*A* shows that the volume expired after the swallow is influenced by the timing of the swallow relative to the respiratory cycle; the relationship is similar to that shown for expiratory duration (Fig. 5*A*). There was roughly a 1 : 1 relationship ($r = 0{\cdot}77$) between the volume expired after the swallow and the volume during the zero flow phase, as shown in Fig. 6*B*. However, late expiratory swallows tended to be followed by expiratory flow, in some instances bringing the first end-expiratory volume (VEE) after swallowing slightly below the control VEE. The tidal volume of the first breath

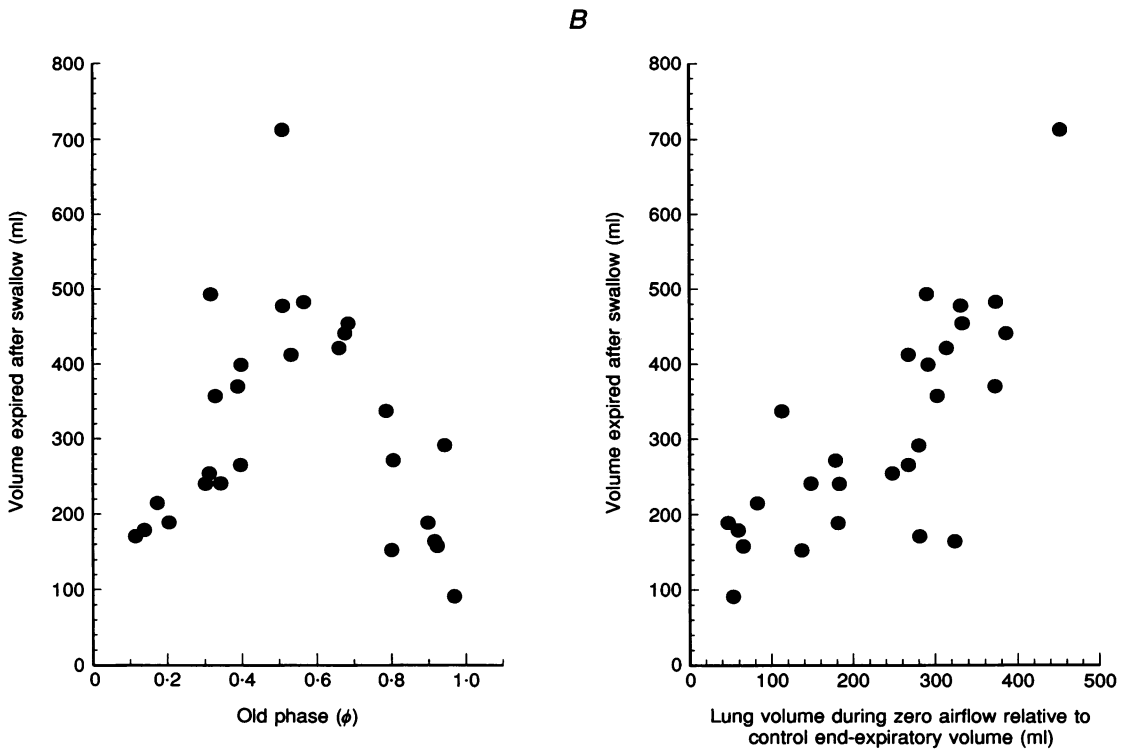

Figure 6. Volumetric changes associated with swallowing in subject O.S.

A, the volume expired after swallowing is dependent upon the respiratory phase of swallow initiation, with maximum volume expired for swallows initiated at the I–E phase transition, and minimum volume expired for I–E swallows. *B*, volume expired is related ($r = 0{\cdot}77$) to the volume during deglutition apnoea relative to end-expiratory volume of control breaths.

after swallowing was larger than the control tidal volume (mean increase 51 ml, $P < 0{\cdot}05$).

We compared the airflow changes with spontaneous swallows ($n = 218$ swallows) to those due to 5 ml bolus injection. The intervals of deglutition apnoea during spontaneous swallows were shorter than for 5 ml bolus swallows, by an average of 534 ms (range across subjects, 153–1241 ms) for all subjects. This difference was significant for each subject as well as for the group of eight ($P < 0{\cdot}05$). There was a tendency for spontaneous swallows to be followed by shorter expiratory intervals when compared with 5 ml bolus swallows, by an average of 306 ms. However, this difference was significant only in three subjects. In the eight subjects in which airflow was monitored, the mean control period was 4·09 s (range across subjects, 2·7–5·2 s). There was no significant change in the period of the first breath after swallowing compared with the control.

Timing of swallow events relative to the respiratory cycle

Figure 7 provides a diagrammatic representation of the timings of swallowing events relative to the period of deglutition apnoea. The diagram summarizes the results for all eight subjects who swallowed in response to 5 ml injected liquid barium. Submental EMG and zero airflow onsets appear as the earliest events in the swallow sequence, while anterior hyoid movement, bolus transit at the level of the larynx, and pharyngeal constrictor activity occur during the second half of the zero flow interval.

Is the swallow sequence itself affected by the respiratory phase of swallowing? Figure 8 shows that the latency between bolus injection and deglutition apnoea (*A*), and intervals of the swallow sequence (*B*, laryngeal bolus exposure; *C*, pharyngeal contraction; *D*, submental EMG onset to laryngeal bolus departure) were relatively unaffected by the respiratory phase of swallow initiation. The latencies from onset of injection to onset of EMG activity (0·54 ± 0·07 s, 8 subjects) and from onset to peak integrated EMG activity (1·56 ± 0·06 s, 8 subjects) were likewise unaffected by respiratory phase of swallowing.

Because of the constancy of the swallow sequence, a plot of any swallow event to the onset of the next inspiration against old phase should result in a relationship similar to that of cophase; rise and fall with peak values for swallows initiated near the I–E transition, and trough values for E–I swallows. This proved to be the case when we measured the latency from laryngeal bolus departure to onset of next inspiration, which we define as δ. For each of the eight subjects, δ for expiratory swallows was smaller than for inspiratory swallows; the average difference was 485 ms (range 170–885 ms, $P = 0{\cdot}0015$). For the pooled data in all subjects, the trough value of δ occurred at an old phase of 0·79 ± 0·11. The lowest measured value of δ was 495 ms (subject D.T.) for a swallow initiated at an old phase of 0·82.

We also measured the latency between the cessation of inspiration and arrival of the bolus head at the larynx, defined as α. This interval was also phase dependent, being shortest for early inspiratory swallows. For the pooled data in all subjects, the trough value of α occurred at an old phase of 0·23 ± 0·13. The lowest measured value of α was 96 ms (subject O.S.) for a swallow initiated at an old phase of 0·02.

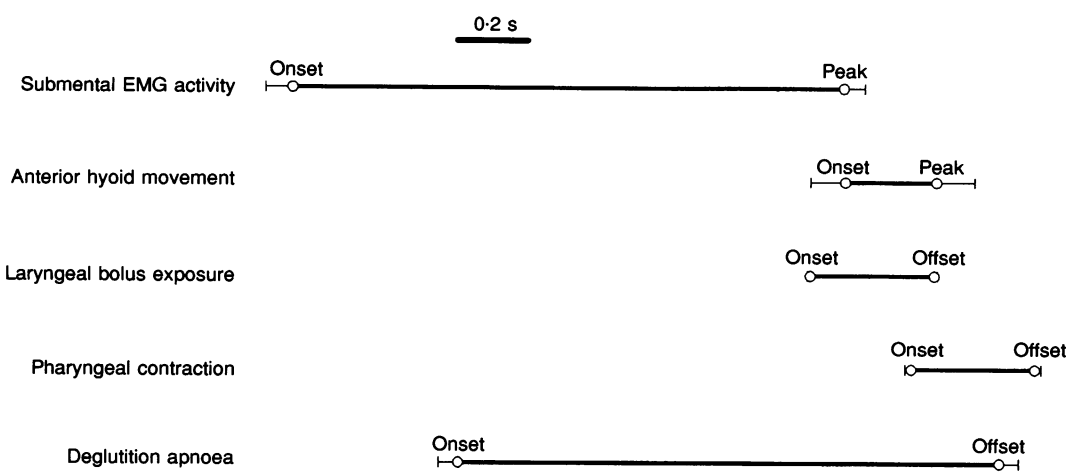

Figure 7. Average time sequence (± S.E.M.) of swallowing events relative to the interval of deglutition apnoea

The onset of deglutition apnoea occurred 466 ± 75 ms (mean ± S.E.M.) after onset of submental EMG activity. Most of the pharyngeal phase of swallowing took place in the second half of deglutition apnoea. Note that the interval between laryngeal bolus departure and end of deglutition apnoea was relatively short (182 ms).

DISCUSSION

This study was designed to evaluate relationships between the timing of respiration and deglutition in awake healthy subjects at rest. We postulated that interactions between the neural generators of the breathing and swallowing cycles would lead to shifts in their phases of activity. Our study provides a systematic description and an interpretation of these phase alterations. We believe that these relationships, in conjunction with anatomical barriers within the upper airway, influence the vulnerability for aspiration during deglutition.

Respiratory phase resetting

Our major finding is that swallowing causes phase resetting of respiratory rhythm. We quantified the pattern of resetting in each subject by plotting the respiratory reset time (cophase) against the swallow onset time relative to the respiratory cycle (old phase). Our measurements were based on the onset of inspiration as the marker of respiratory rhythmicity, and the onset of submental EMG activity as the marker of swallowing. A plot of cophase against old phase revealed a characteristic functional relationship; cophase rises and falls but exhibits a net change of zero over the full cycle of old phase, a pattern which is defined as type 0 resetting (Winfree, 1977, 1980; Paydarfar *et al.* 1986). Use of alternate markers of respiratory rhythm or swallowing resulted in the addition of a constant to all cophase values, without altering the topological features of the resetting plot. The topological properties of phase resetting presented in our study do not reflect a unique mechanism of rhythmicity. Rather, type 0 resetting is a general property of attractor-cycle systems, which exhibit continuous oscillatory dynamics governed by two or more independent state variables (Winfree, 1977, 1980).

We have considered several possible explanations for the finding that cophase was maximum for swallows initiated

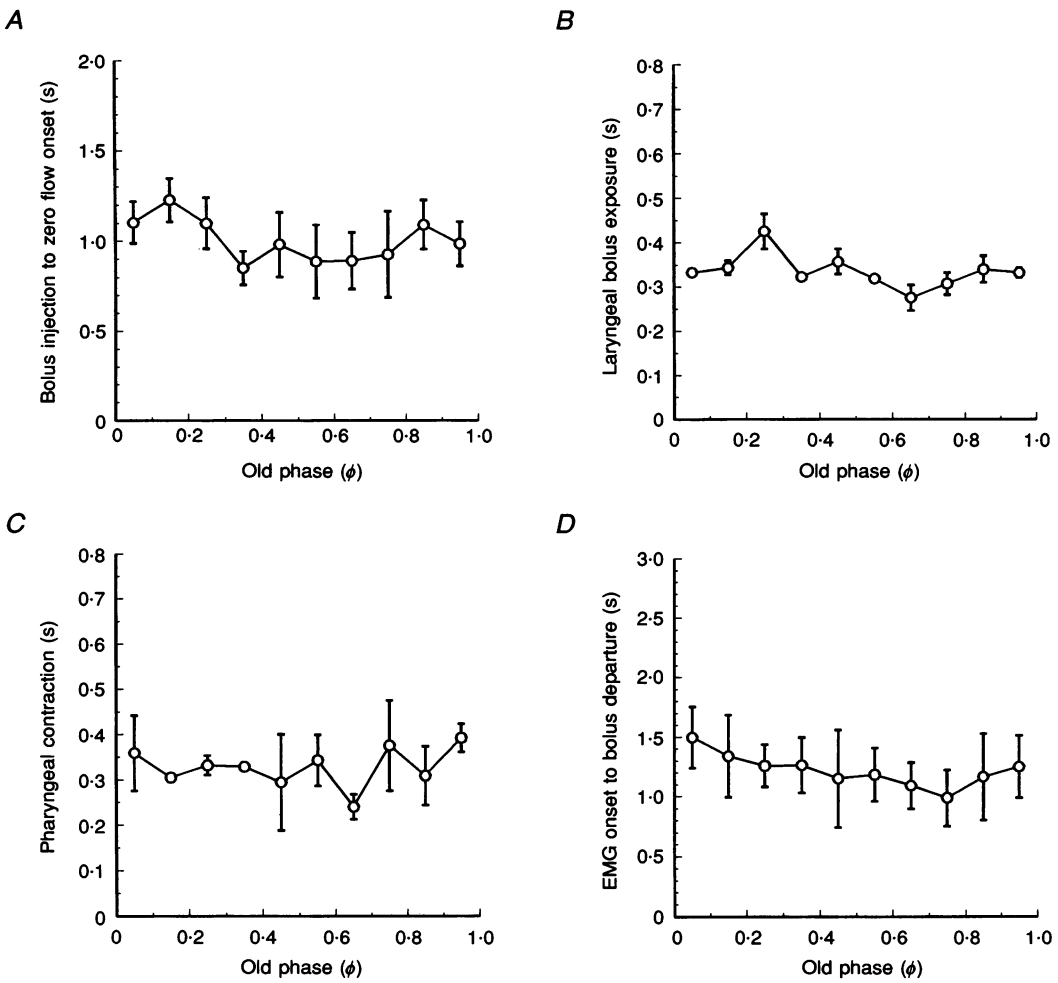

Figure 8. Swallow sequence intervals in eight subjects

The latency between bolus injection and onset of deglutition apnoea (*A*), and intervals of laryngeal bolus exposure (*B*), pharyngeal contraction (*C*), and submental EMG onset to laryngeal bolus departure (*D*). These intervals were relatively constant for swallows initiated at various times in the respiratory cycle.

near the inspiratory–expiratory (I–E) transition period, and minimum for those near the expiratory–inspiratory (E–I) transition. This pattern of variation in cophase, which was found in all subjects, was not associated with changes in the timings of bolus injection, electromyographic activities, pharyngeal contraction or bolus movements within the pharynx. Therefore, it is unlikely that longer reset times were due to more prolonged swallow sequences. One possibilty is that activation of peripheral mechanoreceptors, such as laryngeal or pulmonary stretch receptors, during inspiration or during deglutition apnoea leads to potentiation of the deglutitive neural signal responsible for resetting respiratory activity. This mechanism was proposed by Wilson *et al.* (1981) who found in human infants that the onset of the inspiratory effort after swallowing was longest when the swallow interrupted respiration at the I–E transition period, a time associated with the highest lung volumes. However, it has not been demonstrated that such receptors are activated during normal tidal breaths in adults (Guz, Noble, Trenchard, Cochrane & Makey, 1964). Another explanation is that the variation of cophases is an inherent property of the respiratory oscillator's response to discrete perturbation. Evidence that supports this idea is presented in studies in anaesthetized or decerebrate cats (Paydarfar *et al.* 1986; Paydarfar & Eldridge, 1987; Eldridge, Paydarfar, Wagner & Dowell, 1989) in which respiratory feedback pathways were ablated. Phrenic nerve activity represented 'fictive breathing', without influence from phasic respiratory afferent input. In this preparation, strong (type 0) resetting of respiratory rhythm was achieved using discrete electrical stimuli of the superior laryngeal nerve or midbrain reticular formation. These resetting plots can show variation in cophase as a function of old phase, with peak cophase values at the I–E transition (see Figs 4 and 5 of Paydarfar *et al.* 1986), similar to the present studies. Therefore, phasic peripheral inputs are not required to produce variations in cophase.

Our studies of airflow patterns support the idea that variations in cophase were associated with similar variations in the duration of exhalation after swallowing. The duration of expiration in turn can be associated with changes in lung volume from the time of the swallow to the end-expiratory volume, as shown in Fig. 6. One interpretation of these findings might be that cophase is determined by shifts only in the timing of the mechanical events responsible for exhalation, without resetting of respiratory rhythm. This hypothesis is excluded by our finding that deglutition shifts the timing of all subsequent breaths, suggesting that reset times must reflect changes at the level of the central respiratory rhythm generator, not solely the output system.

Swallowing can be modified by changes in bolus characteristics (Hrycyshyn & Basmajian, 1972; Miller, 1982; Dodds, Man, Cook, Kahrilas, Stewart & Kern, 1988; Dantas *et al.* 1990; Logemann *et al.* 1992; Maddock & Gilbert, 1993). We wondered whether such bolus-related feedback also influences the degree of respiratory resetting by deglutition. Our results demonstrate that modification of the bolus over a physiological range of volume (2–10 ml) and density (barium liquid and thick paste) did not change the pattern of respiratory resetting by deglutition. It is possible that larger volumes or thicker densities would influence respiratory resetting. With regard to larger bolus volumes, Preiksaitis, Mayrand, Robins & Diamant (1992) found that boluses of 20 ml caused greater prolongation of the swallow-associated respiratory cycle than smaller volumes (5 and 10 ml). Regarding swallows of extremely small boluses, we did find that spontaneous swallows (< 1 ml) also caused type 0 resetting of respiratory rhythm but there was a downward shift in the resetting plots when compared with bolus swallows (5 ml). It is uncertain whether these differences were related to the volume differences or to the fact that swallowing was initiated spontaneously rather than in response to bolus injection.

The neural mechanism by which deglutition resets the respiratory oscillator is not known. Deglutition can be induced in animals by electrical stimulation of the anterolateral prefrontal cortex (Sumi, 1969) or by stimulation of superior laryngeal nerve (SLN) afferents (Doty & Bosma, 1956; Miller, 1972), which project to the nucleus tractus solitarii (NTS) and reticular formation (Doty, Richmond & Storey, 1956; Sumi, 1969; Car, 1973). There is evidence that corticofugal and SLN inputs converge on the NTS, which appears to serve as the initial integrative site to potentiate other medullary sites (such as the nucleus ambiguus) involved in the generation of deglutition. The neural signal that links the initiation of swallowing with alterations in respiratory rhythm has not been characterized. Two broad explanations are that: (1) activation of the deglutitive pattern generator within the brainstem in turn causes alteration in rhythm-generating respiratory neurones (Dick, Oku, Romaniuk & Cherniack, 1993); or (2) pathways that facilitate the deglutitive neural generator, such as SLN, corticofugal fibres, and relay sites such as the NTS, cause parallel alterations in respiratory rhythm-generating neurones, without direct influences of the deglutitive generator. At present there is insufficient evidence to make a clear choice between these possibilities, or to suggest that both are involved. However, corticofugal inputs are not required because swallowing in decerebrate animals is associated with normal alterations in respiratory timing (Miller & Sherrington, 1916; Hukuhara & Okada, 1956; Sumi, 1963; Altschuler, Davies & Pack, 1987; Dick *et al.* 1993).

Airflow changes during deglutition

Deglutition was associated with a characteristic sequence of oronasal airflow changes: (1) rapid decrease in airflow;

(2) zero airflow interval; (3) brief non-respiratory inward airflow; (4) expiratory interval. The rapid diminution of airflow, coincident with the initiation of the swallowing sequence, led to an interval of zero airflow. The duration of deglutition apnoea was not influenced by the timing of initiation of deglutition relative to the respiratory cycle, and spanned the pharyngeal phase of deglutition in most subjects. Our characterization of the zero flow interval relative to the swallow sequence is consistent with the observation that glottic closure (adduction of the vocal and vestibular folds) is initiated early in the swallow sequence, and remains closed until after completion of bolus transit through the pharynx (Shaker *et al.* 1990). However, glottic closure is not required for deglutition apnoea because it has been recorded in anaesthetized intubated subjects (Nishino & Hiraga, 1991).

The zero flow interval ended in most instances with a brief (< 200 ms) period of air inflow (< 10 ml). We believe this flow was not respiratory because the fluoroscopic images showed that the airway was still closed. This airflow change was coincident with the offset of pharyngeal contraction, when the positive pharyngeal pressure rapidly decreased to become negative for a brief time. Most published recordings of pharyngeal pressure show a similar brief negative pressure deflection (Atkinson *et al.* 1957; Kawasaki *et al.* 1964; Wilson *et al.* 1981; Maddock & Gilbert, 1993), although its mechanism has received little discussion. Atkinson, Kramer, Wyman & Ingelfinger (1957) reported that the negative wave occurred immediately before the pharynx refilled with air, and they suggest that rapid relaxation of the pharynx leads to a partial vacuum. Our findings are consistent with this view. Previous studies of airflow may not have detected brief airflow changes because of slow time responses of the hot-wire technique (Nishino *et al.* 1985), or were not detected because chest wall movement was used as the only measurement of respiration (Smith *et al.* 1989; Shaker *et al.* 1992).

The expiratory interval was influenced by the phase in the respiratory cycle of swallow initiation. It was longest for swallows that began near the I–E transition and shortest for late expiratory swallows. On rare occasions, late expiratory swallows led to a very brief (50–100 ms) expiration or to a full inspiration following the zero airflow interval. Even these swallows induced phase resetting of respiratory rhythm because of the shift in the rhythm related to the zero flow interval.

We compared the airflow changes induced by 5 ml injected boluses with those induced by spontaneous swallows of much smaller fluid volumes (< 1 ml). Spontaneous swallows were associated with significantly shorter intervals of deglutition apnoea, and a tendency for shorter expiratory intervals after swallowing. These findings imply that bolus characteristics have some effect on the timing of airflow changes as well as the amount of phase resetting. Nevertheless, the qualitative changes in airflow and pattern of resetting were the same for spontaneous and bolus swallows.

A number of previous studies have described alterations in respiratory timing in adult subjects who were awake (Clark, 1920; Nishino *et al.* 1985; Smith *et al.* 1989; Selley *et al.* 1989; Shaker *et al.* 1992; Issa & Porostocky, 1994) or anaesthetized and intubated (Nishino & Hiraga, 1991), and in infants (Wilson *et al.* 1981). There is general agreement that swallowing leads to abrupt cessation of respiratory airflow followed by resumption of the pattern of continuous respiration. However, it is not clear from these studies whether deglutition causes phase resetting of respiratory rhythm. Clark (1920) reported that following the apnoeic pause associated with swallowing, respiratory movement resumed 'at the point at which it had been arrested.' Hukuhara & Okada (1956), studying decerebrate cats, stated that after onset of deglutiton induced by injection of water into the pharynx 'the succeeding inspiratory volley is produced at the time when it should be produced normally'. However, recordings with more than one respiratory cycle before and after swallowing were not shown to confirm that phase resetting did not take place. Nishino *et al.* (1985) had concluded that after expiratory swallows, respiratory movement resumed in the same expiratory phase as had been interrupted. However, the respiratory responses shown in their Fig. 1 fulfil our criteria for phase resetting. Other studies in humans (Wilson *et al.* 1981; Selley *et al.* 1989; Nishino & Hiraga, 1991) and in animal models (Miller & Sherrington, 1916; Sumi, 1963; Harding & Titchen, 1981; Dick *et al.* 1993; McFarland & Lund, 1993) concluded that there were shifts in the timing of the first inspiratory cycle after swallowing. It should be pointed out that immediate shifts in firing of medullary respiratory neurones due to deglutition could represent alterations only in bulbospinal output pathways without resetting the respiratory oscillator. None of these previous studies in humans, and only one animal study (McFarland & Lund, 1993) analysed the respiratory rhythm beyond the first breath after a single swallow, a step that would be necessary to prove that the rhythm generator was reset. Several reports show recordings with sufficient length for analysis; we interpret these as showing that the shifts in respiratory timing were due to phase resetting (e.g. Fig. 2 of Nishino *et al.* 1991; Fig. 2 of Shaker *et al.* 1992). Furthermore, neither laryngeal closure nor wakefulness are necessary for the effect because it is apparent in unconscious, intubated subjects (Nishino *et al.* 1991).

Most previous studies found that coincident with onset of the leading complex of the swallow, respiratory airflow was inhibited to zero, marking the beginning of deglutition apnoea. However, Shaker *et al.* (1992) found that three of ten subjects exhibited inspiration before the interval of

deglutition apnoea, which was attributed to Schluckatmung, i.e. swallow-associated diaphragmatic contraction, an early motor accompaniment of the swallow sequence (Vantrappen & Hellemans, 1967). An alternative explanation is that the inspiratory event was triggered by some other stimulus. This possibility would be supported if the onset of the inspiration was actually before the onset of the submental EMG activity, which seems to be the case in their Fig. 1. We found that subjects often inspired if they were exposed to any extraneous cues just before the experimental injection or visual cue. These influences were minimized in our experiments by masking ambient sounds, positioning the subjects to face away from the investigators, and automating the trials. These measures reduced dramatically the likelihood of early inspiratory airflow. However, it should be emphasized that lack of swallow-induced inspiratory airflow does not exclude the possibility of inspiratory effort during deglutition apnoea. In a study in infants (Wilson *et al.* 1981), evidence for obstructed inspiratory effort was found during most swallows.

Issa & Porostocky (1994) have studied the effect of repeated swallows on respiration. Direct comparisons with our results on spontaneous swallowing are limited because they infused water into the mouth at rates that were much larger (up to 40–100 ml min^{-1}) than our continuous infusions (4–6 ml min^{-1}). Nevertheless, we are in agreement that the duration of deglutition apnoea is longer for boluses of greater volume. We have shown in addition that the duration of expiration after deglutition tends to be longer for larger boluses. An inconsistency is their finding that the average duration of deglutition apnoea was 0·25 s for spontaneous swallows without infusion. This is much shorter than our finding of 1·15 s (minimum value 0·41 s) and the durations of deglutition apnoea reported by others (Nishino *et al.* 1985, 1·13 s; Selley *et al.* 1989, 0·6 s; Nishino *et al.* 1991, 0·75 s; Shaker *et al.* 1992, 1·1 s; Preiksaitis *et al.* 1992, 1·9 s). We noticed that many subjects exhibited spontaneous, brief ($< 0·33$ s) episodes of zero airflow and increased submental EMG activity that were not due to swallowing because deglutitive pharyngeal pressure changes were not present. These episodes may have been related to other oral activities such as chewing or sucking and were excluded from our analysis.

Incidence and timing of the swallow sequence

Spontaneous swallows were initiated at all phases of the respiratory cycle, but not with equal probabilities. The majority of swallows were initiated during a period spanning late inspiration through mid-expiration. Few were initiated in late expiration and early inspiration. In contrast, deglutition induced by bolus injection or by visual cues resulted in an equal distribution of swallows across the respiratory cycle. These results suggest that the threshold for initiation of swallowing in awake subjects is influenced by, but not strongly coupled to, the phase of respiration. Most studies in awake adults (Clark, 1920; Nishino *et al.* 1985; Smith *et al.* 1989; Shaker *et al.* 1992; Preiksaitis *et al.* 1992) have reported that spontaneous swallows occurred most frequently in expiration, although Issa & Porostocky (1994) found a greater incidence of inspiratory swallows. The discrepancy in reported findings might be explained by the large number of swallows at the transition between inspiration and expiration; slight differences in detection of the onset of deglutition relative to onset of expiration would lead to large changes in designation of the swallow as 'inspiratory' *versus* 'expiratory'. Furthermore, we have found that measurement of chest wall movement, the sole index of respiration in some studies, does not reliably detect the onset of expiratory airflow.

Inspiratory phasic activity can appear in the base of the tongue, vocal cords, and tensor and elevator muscles of the soft palate. Expiratory phasic activity has been recorded in the superior constrictor muscles of the pharynx (Bartlett, 1986). We hypothesized that respiration-related rhythmic activities might cause phasic changes in the swallow sequence and the timing of glottic closure. However, this hypothesis is not supported in healthy, resting subjects because we found no change in the timing of deglutitive EMG events or bolus movement with respect to timing of the swallow in the respiratory cycle. This constancy of the swallow sequence relative to the respiratory cycle suggests that although respiration-related neural signals may modulate the output of the deglutitive central pattern generator, these influences do not lead to important changes in bolus propulsion or the timing of glottic closure under normal physiological conditions. Kawasaki, Ogura & Takenouchi (1964) came to a similar conclusion with respect to the durations of swallowing-associated oral, pharyngeal and laryngeal EMG activities in awake, resting dogs. It is of interest that they did find that expiratory swallows were associated with larger pressure gradients between the pharynx and oesophagus when compared with inspiratory swallows. However, even if this were the case in humans, we were unable to show any important influences of respiratory timing on the duration of bolus exposure to the laryngeal aditus.

Implications for assessment of airway risk

Laryngeal closure and deglutition apnoea lead to an interval of time during which the bolus can travel through the pharynx without risk of being inspired into the laryngeal vestibule. Therefore, the shorter the time between inspiration (either before or after the swallow) and laryngeal bolus exposure, the greater the risk of aspiration. We have quantified these relationships by measuring the latency between cessation of inspiratory airflow and arrival of the bolus at the laryngeal aditus (α), and the latency between departure of the bolus at the same level and the onset of the next inspiration (δ). Inspiratory airflow after bolus arrival ($\alpha < 0$) or before bolus departure ($\delta < 0$) would be likely to lead to aspiration of at least a

portion of the bolus. We found in all subjects that α and δ were greater than zero, and aspiration was not seen on the fluoroscopic images. Both values were dependent on the respiratory phase of swallowing. In our series the lowest value for α was 0·1 s, and the lowest value for δ was 0·5 s. Minimum values for α were found for inspiratory swallows, and minimum δ values were for late expiratory swallows. We therefore suggest that deglutition near the phase of transition between expiration and inspiration is the most vulnerable for aspiration. It is of interest that spontaneous deglutition in awake subjects is least likely to take place during this putative phase of vulnerability.

We propose that conditions may exist that lead to unmasking of the vulnerable phase and result in overt clinical aspiration. Careful delineation of the timing of bolus movement relative to inspiratory phases may provide information regarding the aetiology of aspiration. For example, brainstem disorders (Wiles, 1991) that might weaken the neural impact of deglutition on the respiratory control system would lead to weaker resetting of respiratory rhythm by deglutition. This results in shorter latencies from the time of laryngeal bolus exposure to the onset of the next inspiration after the swallow, especially when the swallow is initiated near the transition between expiration and inspiration. Penetration of the bolus into the laryngeal vestibule occurs when resetting is so weak that inspiration resumes while the bolus is adjacent to the laryngeal aditus. On the other hand, neuromuscular diseases that affect the pharynx could cause delay in bolus passage without altering the normal pattern of respiratory phase resetting. Aspiration might occur because the delayed bolus is still adjacent to the laryngeal aditus when the normal rescheduled inspiration occurs. We propose that characterization of the pattern of respiratory phase resetting by deglutition could provide important information regarding the aetiology of dysphagia and aspiration.

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